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Kinematic Measurement of 12-week Head Control Correlates with 12-month Neurodevelopment in Preterm Infants

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Abstract

Background—Although new interventions treating neonatal brain injury show great promise, our current ability to predict clinical functional outcomes is poor. Quantitative biomarkers of long-term neurodevelopmental outcome are critically needed to gauge treatment efficacy. Kinematic measures derived from commonly used developmental tasks may serve as early objective markers of future motor outcomes.

Aim—To develop reliable kinematic markers of head control at 12 weeks corrected gestational age (CGA) from two motor tasks: head lifting in prone and pull-to-sit

Study design and subjects—Prospective observational study of 22 preterm infants born between 24 and 34 weeks of gestation

Outcome measures—Bayley Scales of Infant Development III (Bayley) motor scores

Results—Intrarater and interrater reliability of prone head lift angles and pull-to-sit head angles were excellent. Prone head lift angles at 12 weeks CGA correlated with white matter NAA/Cho,

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concurrent Test of Infant Motor Performance (TIMP) scores, and 12-month Bayley motor scores. Head angles during pull-to-sit at 12-weeks CGA correlated with TIMP scores.

Conclusions—Poor ability to lift the head in prone and an inability to align the head with the trunk during the pull-to-sit task were associated with poorer future motor outcome scores. Kinematic measurements of head control in early infancy may serve as reliable objective quantitative markers of future motor impairment and neurodevelopmental outcome.

Keywords

Motor Delay; Kinematics; Preterm Infants

Introduction

Neonatal acute brain injury and specific sequelae of prematurity are known causes of childhood developmental disability [1–3]. Although new interventions treating various etiologies of neonatal brain injury show great promise [4–7], our current ability to predict long-term clinical outcomes following administration of these agents is poor. In neonatal therapeutic clinical trials, the gold standard for motor outcome is neurodevelopmental testing at 18–24 months, which is significantly delayed compared to outcome assessments for adults and older children performed within days of injury. Additionally, early phase therapeutic trials for neonates may be drawn out to 2–3 years and offer no immediate efficacy measures reflecting functional outcomes. Thus, it is critical that we identify surrogate functional biomarkers of long-term neurodevelopmental outcome to gauge the efficacy of current therapeutic interventions used for neonatal acute brain injury [8].

An acceptable biomarker for infant neurodevelopmental outcome would be a test that could be conducted quickly and easily, implemented at most nurseries or pediatric clinics, and able to predict outcome early in the neonatal course [9]. Neurodevelopmental tests such as the Test of Infant Motor Performance (TIMP), Alberta Infant Motor Scale (AIMS), and Bayley Scale of Infant Development III (Bayley) are used in many developmental clinics and specific tasks evaluating postural control, head control, and upper extremity movements are beginning to be examined as potential markers of developmental delay [10,11]. Poor postural control, defined as head lag at 6 months during a pull-to-sit (PTS) task, was recently shown to differentiate low-risk controls from infants with autistic siblings and was predictive of social and communication delay at 36 months, including autism spectrum disorder [10,12,13]. Upper extremity, trunk, and head control determine a young infant's ability to explore his environment and thus promote normal patterns of motor and cognitive development [14,15]; consequently, quantification of head control in early infancy may characterize an essential milestone and serve as a marker of developmental trajectory.

The goal of this study was to develop reliable kinematic markers of head control in early infancy derived from two commonly used motor development tasks, head lifting in prone and pull to sit. Kinematic markers were defined as prone head lift angle and head angle during pull-to-sit (PTS). We hypothesized these two kinematic measures of early head control would correlate with magnetic resonance spectroscopy (MRS) performed near term age, concurrent Test of Infant Motor Performance (TIMP) scores at 12 weeks corrected

gestational age (CGA), and later neurodevelopmental scores on the Bayley Scales of Neurodevelopment III (Bayley) at 12 months CGA.

Methods

Participants

This was a prospective study of 22 preterm infants born between 24–34 completed weeks of gestation (GA) from November 2010 to January 2012. The Institutional Review Board approved this pilot study and consent was obtained prior to enrollment. Exclusion criteria were GA < 24 weeks or major congenital abnormality.

Procedures

Infants were seen for testing at term (TIMP and neuroimaging), 12 weeks CGA (TIMP and kinematic assessment), and 12 months CGA (Bayley). Motor tasks for kinematic assessment were performed at 12 weeks CGA, as development of head control at this age may differentiate infants at high and low risk for delays [11,16]. Neuroimaging data collection was performed at the MUSC Center for Biomedical Imaging. All other assessments were completed at the MUSC Neuromuscular Research Laboratory (MUSC NRL). An experienced pediatric occupational therapist (PCB) with TIMP certification performed TIMP testing and motor tasks for kinematic assessment for all infants to minimize external variability. The prone head lift and PTS tasks used for kinematic analysis occurred over 5–10 min while infants were in a calm, alert state. The same pediatric therapist (PCB), a pediatrician with 30 years experience, and trained research assistants assessed infants using the Bayley III at 12 months CGA (mean: 12.4; range: 11.1 – 13.9) at the MUSC NRL. Bayley assessors were aware of prior TIMP scores when talking with parents about Bayley results, as unblinding of development scores was an Institutional Review Board requirement. However, the same research assistants were blinded to kinematic measures and MR results at developmental testing.

Kinematic Testing and Data Acquisition

Infant participants were placed on a 34" x 18.5" x 2.5" foam mat on a large mat table 18" in height to obtain all measurements related to head control. The mat was labeled with a cross to ensure consistent shoulder and trunk placement in sagittal and coronal planes with the cameras. Colored Duoderm® 1cm² markers were placed over specific anatomical landmarks on the infants, including the right and left temporal window, mastoid process, acromion, iliac crest, and lateral condyles of the femur and ankle. The markers provided visual contrast at the desired landmark to measure angles during the subsequent kinematic data analysis.

Two HDR-HC9 Sony® cameras on tripods were used for video recording and were positioned 36" lateral to the mat (sagittal plane), and 48" from the front of the mat (coronal plane). Dartfish InTheAction® software was used to stream and record each infant's 2 consecutive 20 s prone head lift tasks and 4 consecutive PTS trials. Because prior experience, mood, and fatigue likely influenced the motor tasks assessed, repeated trials on both left and right sides were performed and all trials were used in statistical analyses. All

recordings were captured under participant study numbers and downloaded to a firewall-protected server.

Kinematic Data Analysis

Dartfish® Analyzer software was used for 2D kinematic analysis of recorded movements during prone head lifting and PTS. An infant's prone head lift angle reflected the angle the infant lifted his head and trunk in midline above the mat in prone (Figure 1A). At the start of a 20 s prone video recording, an angle was drawn with one fixed ray parallel to the mat and the second variable ray drawn to the tragus of the ear. This angle had its vertex at the intersection of the mat and a line drawn down from the posterior superior iliac crest (Figure 1A). Dartfish® Analyzer tracked and recorded the infant's head lift angle every 0.05 s over a 20 s clip in an embedded table. If the infant did not keep his head in midline at a particular time point as determined by coronal view, the angle was deleted from the table. Tables were exported to Excel. Average and maximum prone head lift angles were determined for each 20 s trial and means were obtained across the 2 trials.

We measured head angles during PTS as the infant was pulled from supine into a sitting position. For each PTS trial, we measured head angles at 5 standardized trunk angles from the mat. To measure an infant's head angle at a specific trunk angle, we first chose the video frame in which a ray passing through the iliac crest and acromion markers was at an 30°, 45°, 60°, 75°, or 90° angle to the mat (Figure 1B, 90° example shown). A second angle was drawn in this frame to measure the head angle from its vertical alignment with the trunk; this angle had its vertex at the anterior acromion marker, one ray drawn through the center of the temporal window marker (cervical ray), and the second ray drawn through the center of the iliac crest marker (truncal ray). This measured angle was subtracted from 180° to determine the head angle from true head/trunk alignment. If the head angle was 0°, the cervical ray was in line with the truncal ray. This procedure was repeated to measure head angles at 30°, 45°, 60°, and 75° trunk angle to the mat. At a 90° trunk angle during PTS, the infant's head could fall backwards (positive head lag angle, Figure 1B) or forwards (negative head lag angle, Figure 1C). A large deviation from midline in either direction could be abnormal. Thus, absolute values, which disregarded positive versus negative directionality, were used for correlations with outcome measures. Data from all 4 PTS trials and all 5 trunk angles were used for analysis.

In summary, our kinematic dependent variables were: (1) average prone head lift angle, (2) maximum prone head lift angle, (3) head angle at a 30° trunk angle during PTS, (4) head angle at a 45° trunk angle, (5) head angle at a 60° trunk angle, (6) head angle at a 75° trunk angle, and (7) head angle at a 90° trunk angle.

Reliability Analysis

Three examiners performed kinematic analyses to calculate intrarater and interrater reliabilities of prone head lift angles and head angles during PTS. For prone head lift angles, each examiner performed analyses for 3 infants who each had 2 trials for 6 angles total (6/44 = 13.6% of total prone head lift angles coded in the study). For head angles during PTS, each examiner performed analyses at 5 different angles for 3 infants who each had 4 trials

for 60 angles total ($60/440 = 13.6\%$ of total head angles during PTS coded in the study). All examiners repeated 2D kinematic analysis 1 week following the first measurement to determine intrarater reliability. For interrater reliability, three examiners (one experienced, two inexperienced) measured prone head lift and PTS angles as outlined above. Interrater reliability compared head angle measurements from two inexperienced examiners to each other (B–C) and to the experienced examiner A (A–B, A–C) for prone head lift angles and PTS head angles.

Magnetic Resonance Spectroscopy (MRS)

MRS scans were obtained at a mean GA of 42.5 ± 1.6 weeks using a Siemens 3T MR system. Single-voxel ^1H -MR spectra using point-resolved spectroscopy (PRESS) were acquired with a relaxation time of 1.5 s, and signal averages of 128. A single voxel size of $15 \times 15 \times 15$ mm was used for measurements in the basal ganglia (BG) and in the frontal lobe white matter (WM) (Figure 2). Spectra were fit using LCModel with standard Siemens basis sets, with standard deviation (SD) $< 20\%$ as the standard for inclusion of metabolites. The concentration of metabolites NAA, total choline (Cho) and total creatine (Cr) were measured at both short (30 ms) and long (270 ms) echo times (TE), while myo-inositol (mI), glutamate (Glu) and glutamate + glutamine (Glx) were only measured at short TE, due to poor resolution at longer echo times. These metabolites have been shown to be abnormal in white matter injury [17]. Ratios of metabolite concentrations obtained at the same echo times were used for analysis (mI/NAA, mI/Cho, mI/Cr, NAA/Cho, NAA/Cr, Glu/Cr, Glx/Cr). The observed percent of SDs of the lactate signals were too high for inclusion in our analyses.

Outcome Measures

The Bayley Scales of Infant Development are standard tests for measuring infant motor and cognitive neurodevelopment [18]. The Bayley III captures 4 domains of development including cognitive, language, gross motor, and fine motor. Although all 4 domains were administered, only fine motor and gross motor domains were used for analyses for the purposes of this study. Raw scores on both fine and gross motor domains were converted to Z scores corrected for age to obtain Bayley “scaled” gross motor and fine motor scores. If infants had Bayley scaled fine motor or gross motor scores ≤ 8 , they were categorized as having low/below average motor performance; scores > 8 in both scaled motor domains were categorized as having average motor performance [19,20]. Infants’ composite motor scores from the Bayley III were also used for analyses; these scores reflected infants’ fine and gross motor scores combined.

Statistical Analysis

Relationships between kinematic variables and MRS metabolites, TIMP scores, and Bayley scores were examined using Pearson’s correlational coefficient (r) for parametric variables and Spearman rho (r_s) for nonparametric variables. Differences between outcome groups were tested using Fisher’s exact test for categorical variables and Student t test for continuous variables. A multi-level repeated measures model with trunk angle during PTS as the within-subjects factor and Bayley outcome as the between-subjects factor evaluated the

main effects of trunk angle and outcome and assessed if there was an interaction between these two variables. Follow-up analyses were conducted using *t*-tests at each trunk angle with dichotomized motor outcome as the between-subjects factor. Confidence intervals were set at 95% and *p* values < 0.05 were considered significant. Because this was a pilot study and all analyses were exploratory, we did not adjust for multiple comparisons. Final statistics were obtained using SAS 9 (SAS Institute Inc., Cary, NC).

Results

Demographics

Infant demographic information is presented in Table 1. Clinical ultrasound identified 5 patients with intraventricular hemorrhage (IVH), but none with grades III or IV or white matter injury in the form of cystic periventricular leukomalacia (PVL). There were 3 sets of twins and 2 sets exhibited significant twin-twin transfusion.

Nineteen infants were seen for 12-month neurodevelopmental follow-up. Five male and 3 females infants had low/below average motor scores. Gross motor, fine motor, and composite motor scores (*t*-test, *p* = 0.05) and dichotomized motor scores did not differ by sex (Fisher's exact test, *p* = 0.05). For all 19 infants, mean scores were 11.1 for fine motor (SD = 2.7, range 7 – 16), 11.1 for gross motor (SD = 4.2, range 6 – 19), and 106.3 for motor composite (SD = 17.7, range 79 – 136). For the 11 infants with average Bayley motor performance, mean scores were 11.9 for fine motor (SD = 2.0, range 9 – 14), 13.3 for gross motor (SD = 4.1, range 9 – 19), and 115.5 for motor composite (SD = 16.3, range 94 – 136). For the 8 infants with low/below average Bayley motor performance, mean scores were 9.9 for fine motor (SD = 3.2, range 7 – 16), 8.0 for gross motor (SD = 1.9, range 6 – 12), and 93.6 for motor composite (SD = 10.3, range 79 – 112).

2D kinematic measurements of head angles during PTS and prone head lift angles are reliable

Intrarater and interrater reliability of prone head lift angles and PTS head angles at 30 – 90° measurements were excellent (Supplementary Table 1).

Prone head lift angles correlated with white matter MRS NAA/Cho, concurrent TIMP, and future Bayley motor scores

The entire group of 22 infants had an average prone head lift angle of 31.9° (SD = 8.5°, range 12.9 – 47.5) and a mean maximum prone head lift angle of 43.6° (SD = 7.9, range 29.8 – 59.4) at 12 weeks CGA. There were no significant differences in prone head lift angles between males and females. Average prone head lift angle was positively associated with NAA/Cho ratio in the white matter (*n*=10, *r*=0.73, *p*=0.017), and negatively associated with Glx/Cr (*n*=9, *r*=−0.74, *p*=0.023). Higher NAA/Cho is consistent with greater neuronal axon density and less white matter injury.

Average and maximum prone head lift angles correlated with TIMP scores at term (*r*=0.624, *p*=0.003; *r*=0.659, *p*=0.001, respectively) and 12-weeks CGA (*r*=0.788, *p*<0.001; *r*=0.796, *p*<0.001, respectively) (Figure 3A). Average prone head lift angle at 12-weeks positively

correlated with higher 12-month Bayley motor composite ($r=0.546$, $p=0.016$) and gross motor domain scores ($rs=0.607$, $p=0.006$) (Figure 3B). Maximum prone head lift angle positively correlated with 12-month gross motor scores ($rs=0.496$, $p=0.031$).

Infants with average 12-month Bayley motor scores ($n=11$) had an average prone head lift angle of 38.5° (SD = 4.7° , range $31.0^\circ - 47.5^\circ$) whereas infants with low/below average Bayley motor scores ($n=8$) had an average of 25.9° (SD = 4.7° , range $20.6^\circ - 33.5^\circ$) (t-test, $p<0.001$) (Figure 4A). Maximum prone head lift angle was also highly significantly different between outcome groups; those with average Bayley motor scores had a mean maximum head lift angle of 48.8° (SD = 6.1° , range $39.1^\circ - 59.4^\circ$) and those with low/below average scores had a mean maximum head lift angle of 37.3° (SD = 3.1° , range $32.4^\circ - 41.6^\circ$) (t-test, $p=0.001$), (Figure 4B). Infants who had greater prone head lift angles at 12 weeks CGA had better motor scores on concurrent developmental testing and were more likely to have average motor scores at 12 months CGA.

Head angles during pull to sit correlated with TIMP scores

TIMP scores at term and 12 weeks CGA were associated with head angles during PTS at a 90° trunk angle in the first PTS trial. Infants whose PTS head angle deviated most from 0° had lower TIMP scores at term ($r=-0.810$, $p=0.0014$) and 12-weeks CGA ($r=-0.716$, $p=0.0088$). When trunk angles were considered as repeated measures, there were no significant associations between head angle and TIMP scores in individual trials or in all trials combined using repeated measures modeling at term CGA or 12-weeks CGA.

Discussion

New therapies are being developed that address the various etiologies of neonatal brain injury as standalone treatments or adjuncts to hypothermia, including erythropoietin [5], xenon [6], N-acetylcysteine [21], and anti-epileptics [22]. However, to optimize neurologic outcomes in humans, drug treatment regimens need to be refined in early clinical trials [8]. Adaptive clinical trial designs offer the most efficient methods for determining optimal dose for efficacy and safety, but are limited in neonatal trials by a lack of standardized, quantifiable measures to concurrently assess neurodevelopmental outcome. Rather, diagnosis of deficits must wait for 12–24 months for standard tests to identify developmental delay. With such a delay to assess efficacy, the dose or length of therapy cannot be readily adjusted within a trial.

Motor and behavioral tests can be administered very early after injury and give an indication of response to therapy in research studies and developmental progress in the clinic. However, current validated tests are lengthy, complex to administer, and subjective, thus rendering them clinically impractical and too variable for research outcome measures in multicenter trials of therapeutics. In addition, infants who are not identified at birth as being developmentally high-risk are rarely screened in any standardized fashion for developmental delay. Although the American Academy of Pediatrics recommends the use of a standardized developmental screening at each health visit and formal assessments at 9, 18 and 24 months to identify infants at risk for delay/disability, less than 30% of pediatricians surveyed do so routinely, even for infants at highest risk [23–25]. Therefore, identifying quantifiable

markers for normal and delayed development very early is critical for the successful evaluation of infant functional outcomes and for expansion of therapeutics in infants who are at the highest risk for developmental disabilities.

Our findings suggest that kinematic measurements may serve as early, objective markers of motor impairment and neurodevelopmental outcome. Currently, high-speed 3D motion analysis is the gold standard for kinematic evaluation of movement and motor impairment [10]. However, the clinical utility of 3D kinematic analysis is limited due to expensive laboratory set-ups available in a limited number of research centers, non-optimization for infants' small size, and lack of feasibility in a multicenter trial format. Accordingly, we selected simple infant motor movements representative of key developmental milestones that could be performed by any care provider in any nursery or clinic, easily documented by standard 2D video recording in early infancy without special equipment, and analyzed with Dartfish by any trained individual in any location. In this study, a prone head lift angle difference of 15 degrees differentiated high risk from low risk infants. In real time observation, the average clinician or observer does not have the skill to detect such a difference, highlighting the superiority of video analyses relative to clinical observation to detect poor head control. Precisely identifying poor head control may be especially important for infants with mild to moderate brain injury or developmental delay who may otherwise not be screened adequately. Additionally, kinematic video analysis would be easier to implement clinically than acquiring still photographic images at precise positions, which would be far more difficult than identifying the correct position in a stillframe from a recorded video. Our results suggest that short, simple motor movements performed as part of a standard infant evaluation may serve as clinically useful measures of muscle tone and sensorimotor function.

In this study, poor ability to lift the head in prone and an inability to align the head with the trunk during the pull-to-sit task were associated with poor concurrent TIMP scores and low or below average future motor outcome scores. The presence of head lag after four months and poor ability to lift the head while in prone is not characteristic of typical development [10,12,13,26] and may suggest a delay in neuromotor development [11,12,26]. An infant's inability to align the head with the body during the pull-to-sit maneuver or stabilize the head in prone could suggest low or high muscle tone, an imbalance between neck flexors and extensors, poor postural stability, or abnormal sensory processing such as abnormal feedback from the vestibular-ocular righting system [11,12]. Recent studies have also noted the significant impact of poor coupling between early motor patterns and vision in preterm infants and later delays in school related motor responses and visuomotor tasks [27,28]. Furthermore, Karch et al. [29] found that stereotypy scores of upper limb movements in 3-month-old infants identified cerebral palsy cases with 90% sensitivity and 96% specificity at 2 years of age. Because the brain is most responsive to therapeutic treatment early in development, timely identification of motor delay is critical to improve long-term functional outcomes in high-risk infants.

Although 2D kinematic assessments show promise as surrogate markers of functional outcomes, MR neuroimaging is the current gold standard to detect CNS injury in the acute setting. MR imaging is more expensive than cranial ultrasound and is not yet widely used

for clinical diagnosis of brain injury in preterm infants. However, ongoing phase I/II trials focus on MR findings as intermediate markers of brain injury in newborns (www.npeu.ox.ac.uk/toby-xe) and thus we compared our kinematic measures with known MRS indices of injury [8]. Although our sample size for MR imaging was limited by funding, the preliminary results are encouraging that quantitative measures of head lift in the prone position may reflect metabolically healthy neurons and axonal density and integrity with higher NAA/Cho ratios. Other limitations of our study include the need for larger sample sizes in future studies to determine the sensitivity, specificity, positive and negative predictive value of these kinematic measurements and to assess the validity and reliability of these measures in full term infants, particularly those with brain injury.

Even though MR imaging is the gold standard to detect acute CNS injury, functional markers of early motor delay are essential for clinical use. Both our data and that of other investigators suggest early motor delays may reflect poorer later neurodevelopmental outcomes [12,13]. Brain plasticity and recovery from preterm birth or injury may be captured real time with the quantitative kinematic measures described here, and used to track individual infants' progress over time. With further validation of these measures in larger populations, we may move towards quantifiable, accurate developmental screening early in the first year of life, before abnormal patterns of movement become pathologic. Early identification of motor delays is essential to assure timely initiation of early intervention services while there is potential to change an infant's developmental trajectory. With promising neurotherapeutics in the pipeline, the need for quantifiable measures of efficacy in early infancy is compelling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

CGA	corrected gestational age
IVH	intraventricular hemorrhage
PVL	periventricular leukomalacia
MRS	magnetic resonance spectroscopy
mI	myoinositol
NAA	N-acetylaspartate
Cr	Creatine
Cho	choline

Glx glutamine + glutamate

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Research Article Highlights

- Kinematic markers were derived from pull-to-sit and prone-head-lift motor tasks.
- Head angles during pull-to-sit correlated with concurrent motor scores at 12 weeks.
- Prone head lift angles correlated with future motor scores and white matter NAA/Cho.
- 2D kinematics may provide quantitative measures of development early in infancy.

Figure 1. Kinematic analysis of prone head lift and pull-to-sit tasks using Dartfish®. Anatomical markers: I = posterior iliac crest, II = tragus, III = temporal window, IV = acromion process, V = anterior superior iliac crest

1A. Maximum prone head lift angle measured with Dartfish® Analyzer tracking tool. An embedded Dartfish® Analyzer data table is shown.

1B. Head angle at a 90° trunk angle during pull-to-sit measured with Dartfish® Analyzer tracking tool.

1C. Head angle at a 90° trunk angle during pull-to-sit measured with Dartfish® Analyzer tracking tool.

Anatom

Figure 2.
A 15 mm^3 voxel box was placed in the basal ganglia (BG) and frontal white matter (WM) for magnetic resonance spectroscopy data acquisition.

Figure 3.

Relationships between average prone head lift angle and motor developmental tests.

Average prone head lift angle was associated with TIMP at term and 12 weeks CGA (A) and Bayley gross motor scores at 12 months CGA (B).

Figure 4.
Average (A) and maximum (B) prone head lift angles by 12-month dichotomized motor Bayley outcomes.

Table 1

Patient demographics.

	Females <i>n</i> =10	Males <i>n</i> =12	Total <i>n</i> =22
<i>Race</i>			
African-American	7	4	11
Caucasian	3	8	11
<i>Entry Strata</i>			
Mean gestational age at birth (SD), wks	29.1 ± 3.2	30.1 ± 2.7	29.6 ± 2.9
Mean birth weight (SD), g	1138 ± 672	1359 ± 611	1259 ± 634
<i>Clinical Characteristics</i>			
Maternal diabetes, <i>n</i>	1	1	2
Intrauterine growth restriction (< 10%), <i>n</i>	5	4	9
Occipital frontal circumference (< 10%), <i>n</i>	6	5	11
Intracranial lesions, <i>n</i> :	4	1	5
Intraventricular hemorrhage grade I	3	0	3
Intraventricular hemorrhage grade II	1	1	2
Periventricular leukomalacia	0	0	0
Infarcts	0	0	0
Hypoxic Ischemic Encephalopathy, <i>n</i>	1	1	0
Patent ductus arteriosus (medically treated), <i>n</i>	3	4	7
Bronchopulmonary Dysplasia, <i>n</i>	4	5	9
Infection, <i>n</i> :			
Blood culture sepsis	2	1	3
Pneumonia,	0	1	1
Urinary tract Infection	0	1	1
Chorioamnionitis	0	2	2
<i>TIMP risk category</i>			
<i>At term CGA, n</i>			
High risk	4	4	8
Low risk	6	7	13
<i>At 12-weeks CGA, n</i>			
High risk	4	5	9
Low risk	6	7	13
<i>Bayley III Motor Outcome, n</i>			
Low/below average (Gross motor < 8)	3	5	8
Average	4	7	11